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Blastogenesis Dominant 1: A Sequence With Midline Anomalies and Heterotaxy

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Lateralization defect is a heterogeneous condition with different modes of transmission (autosomal recessive, dominant or X-linked). Here, we report on 3 additional families that contribute to the description of phenotypic anomalies of the autosomal dominant type. Phenotypic anomalies include: lateralization defects, cardiac malformations, diaphragmatic hernia, urologic and neurologic anomalies. We suggest calling this sequence BGD1 for blastogenesis dominant 1 because the deleterious effect probably occurs during blastogenesis and involves not only lateralization but other defects as well. Am. J. Med. Genet. 68:405–408, 1997.

KEY WORDS: lateralization defect; midline; cardiac malformation; autosomal dominant; blastogenesis

INTRODUCTION

Lateralization defects include malpositioning of thoracic and/or abdominal organs. This condition was called heterotaxia (or heterotaxy) because this is the exact meaning of these Greek words (heteros, different, and taxos, positioning). This is a heterogeneous condition and initial attempts to sort out the different components relied on phenotypic data. Although it was important to list most of the phenotypic anomalies associated with lateralization defects pertaining to the medical perspective of affected individuals, it was irrelevant to cause since familial cases [Simpson and Zellweger, 1973; Arnold et al., 1983; Zlotogora et al., 1987] and animal models [Hummel and Chapman, 1959; Yokoyama et al., 1993] showed a very variable phenotypic expression irrespective of the anatomic groups. Another approach aimed at dissecting the lateralization events might be to identify mendelian transmission types. Besides the common autosomal recessive heterotaxy, there are rare cases of X-linked [Soltan and Li, 1974; Fullana et al., 1986; Mathias et al., 1987; Mikkilä et al., 1994; Casey et al., 1995] and autosomal dominant transmissions [Niikawa et al., 1983; Chen and Monteleone, 1977; Alonso et al., 1995; Lindor et al., 1995]. Here, we present 3 new pedigrees which contribute to delineate the autosomal dominant sequence. Because these defects involve not only lateralization anomalies but also midline anomalies, they probably disrupt the normal blastogenesis process and we suggest calling them Blastogenesis Dominant 1 sequence (BGD1).

CLINICAL REPORT

Family 1

This family includes 2 affected members in 2 generations (Fig. 1).

Individual I-2. At age 21, he was discovered to have a bilateral hydronephrosis with urolithiasis, partly incorporating a piece of kidney parenchyma on the left side. The hydronephrosis was caused by bilateral obstruction of the pelviureteric junction. He underwent numerous procedures to remove stones and to alleviate the urinary obstruction. Microscopy of the right pelviureteric junction obstruction showed scattered sclerosis and fragmentation of elastic fibers. No lateralization defect was noted on roentgenograms and ultrasound examinations of the chest and abdomen and no extrinsic compression was evidenced at the level of the pelviureteric junction.

Individual II-1. The son of individual I-2 has a complete situs inversus and bilateral pelviureteric junction obstruction. The later anomaly was discovered at age 4 years because of painful kidney stones.

The brother of I-2 has no anomaly. Their parents died while both brothers were young. Because of the family history, the younger brother of II-1 had an intravenous urography which demonstrated a normal urogenital tract. The mother of II-1 and II-2 is normal.

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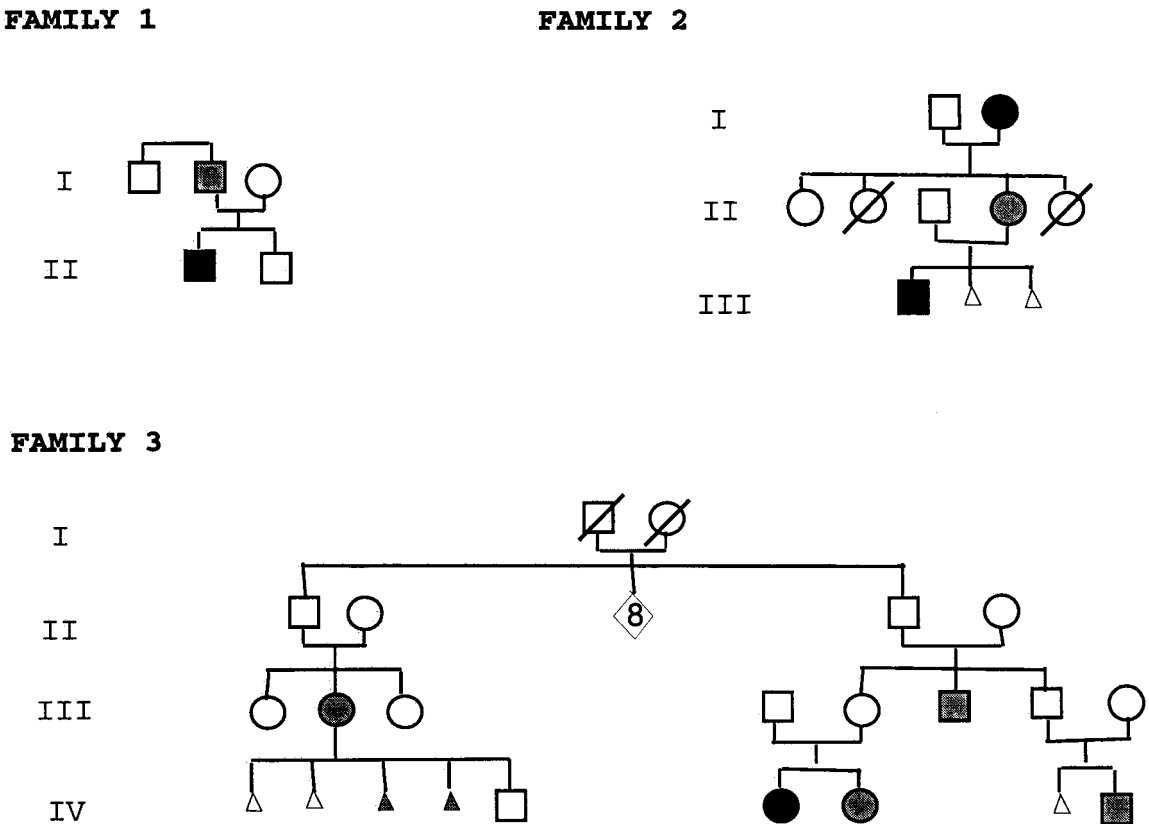

Fig. 1. Presentation of pedigrees. Filled symbols represent females (circles) or males (squares) with lateralization defects. Shaded symbols are individuals with midline or other dysgenesis defects. Crossed symbols represent deceased persons. Abortions are represented by open small triangles.

Family 2

Individual III-1. Fetal ultrasonography was unremarkable until 33 weeks, when a complex heart defect, diaphragmatic hernia and polyhydramnios were detected. The patient was born vaginally at 34 weeks from a vertex presentation. Birth weight was 2150 g (50th centile), length 47 cm (75th centile), and head circumference 34 cm (OFC) (75th–90th centile). In spite of resuscitation, he died 2 hours after birth.

Autopsy showed complex cardiovascular malformations (single atrium right of type, mitral valve atresia, left ventricular hypoplasia, ventricular septal defect, right ventricular hypertrophy, and aortic arch atresia), agenesis of the left hemidiaphragm with hypoplasia of the left lung and herniation of left hepatic lobe, stomach, small intestine, and part of colon and pancreas. In addition, he had horseshoe kidneys and asplenia. Chromosomes were apparently normal (46,XY).

Individual II-4. Mother of individual III-1 (Fig. 1) is asymptomatic but she was requested to undergo an abdominal ultrasonography because of her son's history. She has a displacement of the left kidney under the right one with a probable partial fusion (crossed fused ectopia).

Individual I-2. For unknown reasons, in 1990 the maternal grandmother of the propositus had in 1990 an intestinal tract contrast radiography which showed an intestinal malrotation. This finding was later confirmed by another radiographic examination. Abdominal ultrasonography did not disclose any other anomaly.

The mother of the propositus had 2 additional pregnancies. The first one ended with a miscarriage at the 11th week, and the second one was terminated for trisomy 21. One maternal aunt (II-2), delivered at home prematurely (6th month of gestation), died at birth. No other information is available. Another daughter (II-5) was also born prematurely (7th month of gestation), presented cyanosis at birth and died after 2 days. No necropsy was performed. A third maternal aunt is living and has no abdominal or thoracic anomaly evidenced by ultrasound examination. The father and the maternal grandfather are normal.

Family 3

Individual IV-6. She has abdominal heterotaxy with a midline liver, inverted rotation of the intestinal tract and a small spleen on the right. At birth, she had a small ventricular septal defect which closed spontaneously. Because of pyelonephritis, she had urography which showed a vesicoureteral reflux on the right side. The kidneys were normal but the right ureter was medially positioned. A radiographic examination for lumbar pain showed a bilateral spondylolysis of the fifth lumbar vertebra with a mild spondylolisthesis. After a

car accident, she had a CT scan which disclosed a somewhat enlarged posterior fossa which suggested to geneticists that she might have a mild variant of Dandy-Walker syndrome. In addition, she has epicanthal folds and telecanthus (97th centile).

Individual IV-7. The younger sister of IV-6 (Fig. 1). She has epicanthal folds, telecanthus, bilateral internal strabismus and lateral nystagmus in maximal adduction. On the right eye, a nevus of the choroid was observed close to the macula. An MRI demonstrated agenesis of the posterior ⅔ of corpus callosum (Fig. 2). She had moderate hypotonia of lower limbs with a mild instability on walking. An ultrasound examination ruled out any thoracic, intestinal or urinary defects. Chromosomes were normal (46,XX).

The clinical findings, chest roentgenogram and abdominal ultrasound of the parents were normal.

Individual III-6. A maternal uncle has telecanthus and epicanthic folds, whereas another maternal uncle has a son with soft palate cleft, telecanthus, tetralogy of Fallot, and mild mental retardation. His parents (III-7 and III-8) have no telecanthus or epicanthic folds.

Individual III-2. She had a ventricular septal defect. She had 5 pregnancies: 2 miscarriages for unknown reasons, 2 pregnancy terminations (one due to anencephaly and the other due to a severe cardiac malformation) and a normal child.

DISCUSSION

Four reports have already described families with multiple cases of lateralization defects segregating as an autosomal dominant trait [Niikawa et al., 1983; Chen and Monteleone, 1977; Alonso et al., 1995; Lindor et al., 1995]. Moreover, Alonso's [Alonso et al., 1995] and Casey's studies [Casey et al., 1993] suggested that a cardiac malformation might be the only expression of a lateralization defect. Besides lateralization and cardiac defects, some other anomalies are consistently observed in these families with a dominant inheritance. Individual III-1 of family 2 and individual III-1 of family 1 in a previous report [Alonso et al., 1995], had both a diaphragmatic hernia. Five affected individuals in this presentation had urologic anomalies including kidney displacement and fusion, pelviureteric junction obstruction, and vesicoureteral reflux. All of these anomalies were described previously in association with lateralization defects [Rodríguez et al., 1991; Mac Taque et al., 1992; Martínez-Frías et al., 1995]. In addition, lateralization defects are more frequent in infants with midline defects than without [Martínez-Frías et al., 1995]. The fact that multiple organs are involved together with midline and lateralization anomalies strongly suggests that this defect occurs before organogenesis, or in other words during blastogenesis [Opitz, 1993]. Whereas in pathologic studies, anomalies have to be concomitantly observed in individuals to demonstrate an association, in family studies, affected individuals do not usually present the whole spectrum of anomalies but a limited number of features which differ from an affected individual to another. In addition, family studies shed new light on the phenotypic variability and the mode of transmission. These two points are of much importance in order to correctly interpret family history and guide genetic counseling. Since the expressivity of these defects seems to be extremely variable even within a family, one should not consider these familial cases to be a coincident occurrence of different genetic defects but rather different expressions of the same defect. Although clinical categorization is important for therapeutical strategies, the causal classification does not have to be identical. Finally, it is worthwhile noting that there seems to be an increase in the defect severity in successive generations. If these anomalies constitute a syndrome, then it could suggest that it is subjected to anticipation, a phenomenon already described in some other dominant syndromes [Mandel, 1994; Asley et al., 1995].

Because this condition associates lateralization and midline defects which suggest a defect during blastogenesis, we propose calling this sequence Blastogenesis Dominant 1 or BGD1. In fact, there is no reason to call this sequence "dominant heterotaxy" since organ malposition is not an obligatory anomaly. So far, there is no evidence to demonstrate that all BGD1 cases are related to mutations in a single gene which preclude the use of the word "syndrome."

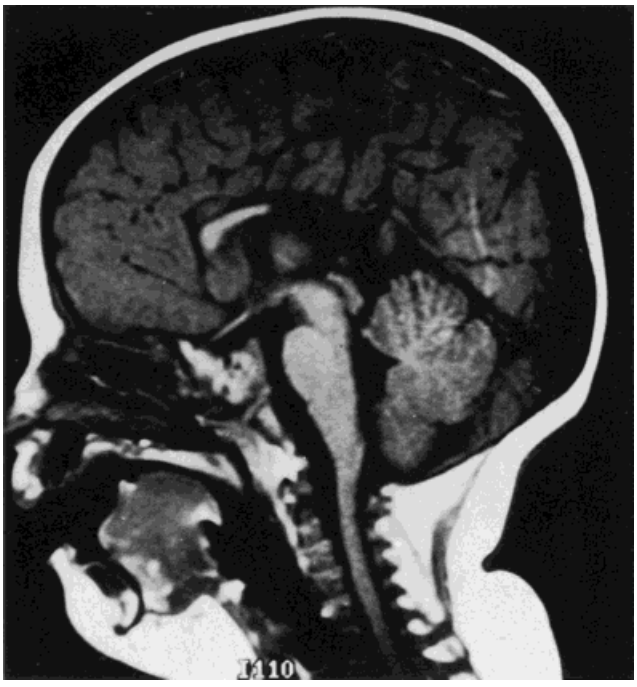

Fig. 2. MRI profile of individual IV-3 of family 3 shows absence of the mid and posterior portion of the corpus callosum.

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